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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/974,974	TAIRA ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-03, 3-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 10-1-04.

Claims 1-30 are pending in the instant application.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Election/Restrictions

Applicant's election with traverse of the dimer pair of claim 9 (comprising SEQ ID Nos: 1 and 2), the promoter of SEQ ID NO: 5, and the target gene of an mRNA encoding a protein associated with a disease such as cancer, in the reply filed on 10-1-04 is acknowledged. The traversal is on the ground(s) that a search of all of the claims, including other dimer pairs (SEQ ID Nos: 3 and 4) and target genes would not pose a serious burden on the examiner. Applicants also argue that a search that established the patentability of one dimer pair would establish the patentability of all sequence combinations comprising that dimer pair. This is not found fully persuasive because a search of one dimer pair would not establish the patentability of the other dimer pair. A search for the invention of claim 9 would not encompass a proper search for the invention of claim 11, which comprises different and distinct dimer pairs. The inventions of these different and distinct dimer pairs together would impose a serious search burden. The search of the different and distinct two dimer pairs are not coextensive.

And in cases such as this one where descriptive sequence information is provided, the sequences are searched in appropriate databases. The search of the instant invention requires an extensive analysis of the art retrieved in a sequence search as well as in depth technical searches of the patent and non-patent literature for the generic claims. A search for the dimer pair of claim 9 would not likely result in relevant art with respect to the dimer pair of claim 11. Applicants are correct that if the elected primer pair is found free of the prior art within the context of the claimed invention, then the promoter would be free of the prior art. Therefore, claims 1-10, 12-30 are examined in the instant Office action, claim 11 (comprising primer pairs of SEQ ID Nos: 3 and 4) is withdrawn from consideration as being drawn to a non-elected invention, and the claims drawn to different promoters, target genes and linking sequences have been rejoined and are examined in the Office action as indicated below.

Claim 11 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10-1-04.

The requirement is still deemed proper and is therefore made FINAL.

The restriction requirement mailed 7-1-04 did not state that claims 1 and 2 were being treated as linking claims. In order to provide Applicant with the opportunity to have claims 1 and 2 examined as part of the elected invention, claims 1 and 2 have been examined as linking claims in the Office action set forth below. In addition, each of the dimer pairs claimed comprise a distinct and different invention, and the election of

SEQ ID Nos: 1 and 2 has been treated as an elected invention, not a species election. These different and distinct oligonucleotide pairs, with different SEQ ID Nos, are considered to be structurally independent, because each is represented by a unique nucleotide sequence and each represents a different and specific oligonucleotide. Furthermore, a search of all the dimer pairs claimed presents an undue burden on the Patent and Trademark Office to search and examine. In view of the foregoing, Applicants' election of SEQ ID Nos: 1 and 2 as the elected invention is acknowledged.

Claims 1 and 2 link(s) inventions comprising SEQ ID Nos: 1+ 2, and 3 + 4. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claims 1 and 2. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Information Disclosure Statement

The European Search Report for Application No. EP 01 30 8694 has been considered but it has been crossed out on the 1449 form because it is not a citation for a reference and so will not be cited as a reference on a published patent.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 and 12-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, lines 3-4, it is unclear what is meant by the term "RNA, DNA or protein different from the target RNA." Does this mean that the nucleotide sequences of the target site and sensor site are different, but may still be from the same molecule? Does this mean that a protein encoded by the target RNA must be different from the RNA or DNA that binds to the sensor site, or that, since a protein is different from RNA, a sensor could bind to a protein that is encoded by a target RNA, as long as it is expressed protein, and not a nucleic acid encoding it? Appropriate clarification is requested.

In claim 2, line 15, "said RNA" is unclear since RNA is previously mentioned in several contexts in this claim, and in claim 1 from which it depends (e.g. as target RNA and to bind to a sensor site). Appropriate clarification is requested.

Regarding claim 4, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

In claim 14, it is unclear if the sequences in lines 3-4 [depicted as (5) and (6)] are additional sequences in the nucleic acid enzyme construct, or instead constitute part of the linker or promoter described in claim 12. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to nucleic acid enzymes having a sensor site and a cleavage active site, wherein cleavage occurs only when the target RNA binds to the cleavage active site while DNA, RNA or protein (e.g. nucleotide sequences other than the target RNA) bind to the sensor site. The nucleic acid enzymes optionally comprise

the formula depicted in claim 2, and the target RNA optionally encodes any protein essential for cell survival, or encodes a disease associated protein, and which sensor site optionally comprises a tissue or time-specifically expressing mRNA. Furthermore, the nucleic acid enzymes optionally comprise a dimeric structure comprising SEQ ID Nos: 1 and 2, or wherein nucleotide NOs. 1-9 and 19-27 of SEQ ID NOs: 1 and 2 respectively may or may not be modified such that they are complementary to a target RNA which is adjacent to a target RNA cleavage site. The specification and claims do not describe elements that are essential to various genera comprising *sensor sites* (including time or tissue specific in their expression), *proteins essential for cell survival, disease-associated proteins, disease-causing abnormal mRNA,* or *mRNA specific to an AIDS-causing virus*. Nor do the specification and claims adequately describe the broad genera comprising *nucleic acids encompassed by the formula in claim 2*, nor how the dimeric structure of claim 9 *is or is not modified to include other target RNA sequences*, or how this dimeric structure fits in structurally with the formula claimed in claim 2. In addition to lacking essential elements to describe these very broad genera, the specification and claims do not indicate what distinguishing attributes are concisely shared by the members of these various genera. The scope of the claims includes numerous structural variants (e.g. a myriad of possible sequences), and the genera are highly variant because a significant number of structural differences between members of a given genus is permitted. Concise structural features that could distinguish structures or compounds within a given genus from others are missing from the disclosure. No common structural attributes concisely identify the members of the

genera and the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed (*see e.g.* Araki et al, Nucleic Acids Res., Vol. 26, No. 14: 3379-3384, 1998, abstract on p. 3379 and text on pp. 3383-3384 (provided in the IDS filed 3-25-04) describing variable cleavage capabilities of allosteric ribozymes, which depends on the size and structure of the ribozyme loops, and whose function and control depend on a multitude of factors, including the binding site (sensor site) for the effector molecule (e.g. flavin allosteric effector) and the ribozyme structures required to achieve proper conformation for attaining allosteric control and/or cleavage activity). The specification and claims fail to teach or adequately describe a representative number of species in each genera such that the common attributes or characteristics concisely identifying members of each proposed genera are exemplified. And because each genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the various genera claimed. Thus, Applicant was not in possession of the claimed and very broad genera.

Claims 1-10, 12-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods for cleaving target mRNA in vitro following administration of the particularly described CML, HIV and tRNA Val T-MZL/R maxizymes , does not reasonably provide enablement for compositions and methods for cleaving any target genes in vitro or in vivo comprising the

administration of any maxizyme of any sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions (including diagnostic compositions) and methods for cleaving any target RNA in vitro or in vivo using any nucleic acid enzyme having a sensor site and a cleavage active site, wherein the nucleic acid enzyme has cleavage activity towards the target RNA only when the target RNA binds to the cleavage active site while an RNA, DNA or protein (different from the target RNA) binds to the sensor site, and which compositions are used in prevention and/or treatment of any disease caused by any target DNA, and which compositions control or inhibit expression of any disease-causing abnormal mRNA.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate that the field of allosteric enzymatic RNA (*a.k.a.* maxizymes) (and their use in gene therapy) is still in its infancy. Araki et al (Nucleic Acids Res., Vol. 26, No. 4: 3379-3384, 1998, at the abstract on p. 3379 and text on pp. 3383-3384) (provided in the IDS filed 3-25-04) teach variable cleavage rates and variable allosteric control of a series of maxizymes, where different sequences provided for different conformations, some of which were enzymatically active, some of which were allosterically regulated, and some of which were enzymatically inactive or non-allosterically regulated. Tanabe et al (Biomacromolecules, Vol. 1 : 108-117, 2000, abstract and text on pp. 108-109, text on p. 110) (provided in the IDS filed 3-25-04) teach the generation of active and inactive

maxizymes in attempting to design nucleic acid enzymes with optimal conformations that provide for allosteric control of target gene cleavage upon sensor binding. Tanabe et al also teach the unpredictability of unpaired sequences in these maxizymes and the effect on allosteric and enzymatic capabilities of the maxizymes (*Id.*, bridging paragraph on pp. 113-114).

The following references are cited herein to illustrate the state of the art of nucleic acid treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text of A. Branch, Trends in Biochem. Sci., 23, 45-50, 1998; and S. Crooke, Antisense Res. & Application, Chapter 1, pages 1-50, ed. by S. Crooke, Springer-Verlag, especially pages 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches: "Much progress has been made towards understanding the structure and mechanism of these catalysts [ribozymes]...Despite this, it is not yet clear whether these molecules can be developed into clinically useful pharmaceutical preparations." (See Peracchi et al, Rev. Med. Virol., 14, pages 47-64, 2004, abstract on page 47). Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter

the cells where they are supposed to operate... cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (*Id.*, text on page 51)

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (Tamm et al., The Lancet, 358: 489-497, 2000, see pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (Agrawal et al., Molecular Med. Today, 6: 72-81, 2000 at pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al, Biomaterials, 23: 321-342, 2002 in its entirety, especially pages 326-327 for

a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. The specification teaches the in vitro cleavage of target genes using CML (p. 26 of the specification), HIV (pp. 25-26 of the specification, figure 8), Bcl2 (fig. 10 and p. 28 of the specification) and tRNA Val T-MZL/MZR (fig. 7A) maxizymes. The prior art (Tanabe et al, Nature, Vol. 406: 473-474, 2000) teaches the transduction of a particularly described maxizyme targeting VCR-ABL mRNA into tumor cells in vitro, then injecting these transduced tumor cells into NOD/SCID mice in vivo (for more details, see the 102 rejection below).

Applicants have not provided adequate guidance in the specification, however, for the ability to target and specifically cleave any target gene in vitro or in vivo using any maxizymes (e.g. of any nucleotide sequence) that comprise any sensor site and any target site, whereby allosteric regulation and specific cleavage is obtained in vitro or in vivo. Applicants have not provided adequate guidance for the administration and delivery of any maxizyme to target cells in vivo.

One skilled in the art would not accept on its face the examples given in the specification of the in vitro cleavage of target genes using the CML, HIV, Bcl2 and tRNA Val T-MZL/MZR maxizymes (and particularly described in the specification), or the example of transducing tumor cells in vitro then injecting transduced tumor cells into NOD/SCID mice, as being correlative or representative of the ability to achieve target cell delivery, and subsequent allosteric control and target cleavage in vivo. Nor are

these examples representative of the ability to design maxizymes comprising any sensor site and any cleavage active, whereby allosteric control and target cleavage is obtained in vitro or in vivo, including for any nucleic acid molecule comprising the formula in claim 2, or comprising SEQ ID Nos: 1 and 2, whereby nucleotide nos. 1-9 and 19-27 of SEQ ID Nos: 1 and 2 respectively may or may not be modified such that they are complementary to any target RNA adjacent to any target RNA cleavage site, or wherein nucleotide nos. 20-32 and 1-12 of SEQ ID NOs: 1 and 2 respectively may or may not be modified with another mRNA specific to an AIDS-causing virus, HIV-1 or to another site within tat mRNA of HIV-1. There is a lack of guidance in the specification and an unpredictability associated with the successful design of allosteric RNA enzymes whereby the proper conformation is attained in vitro or in vivo for cleavage specificity and allosteric control, as well as an unpredictability associated with the ability to deliver maxizymes to appropriate target cells in an organism, and further whereby such molecules are sufficiently delivered to the target cells in vivo, maintain their allosteric regulatory capacity, and specific target gene cleavage is obtained and treatment effects are provided.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to compositions (including diagnostic compositions) and methods for cleaving any target RNA in vitro or in vivo using any nucleic acid enzyme having a sensor site and a cleavage active site, wherein the nucleic acid enzyme has cleavage activity towards the target RNA only when the target RNA binds to the cleavage active site while an RNA, DNA or protein (different from the target RNA) binds to the sensor

site, and which compositions are used in prevention and/or treatment of any disease caused by any target DNA, and which compositions control or inhibit expression of any disease-causing abnormal mRNA.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of nucleotide sequences encoding nucleic acid enzymes having any sensor site in combination with any cleavage active site that target, specifically cleave, and inhibit expression of any target RNA, including any disease-causing, abnormal mRNA, whereby allosteric control is obtained for any combination of sensors and targets and specific target gene cleavage is obtained in vitro and in vivo, and any disease caused by any target DNA is prevented and/or treated. Other experimentation required to practice the invention over the scope claimed includes the determination of appropriate target cells harboring the target gene and sensor molecule, determination of accessible target sites, modes of delivery and formulations to target these appropriate cells and /or tissues, whereby maxizymes are successfully delivered, are allosterically controlled and specific target gene cleavage is achieved. Since the specification fails to provide sufficient guidance for the in vivo targeting and cleavage of the broad array of target molecules claimed (e.g. including any disease-causing mRNA), using enzymatic nucleic acids comprising of any target gene binding site in combination with any sensor molecule, and since the specification fails to provide adequate written description for the broad genus comprising the enzymatic nucleic molecules (maxizymes) claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-8, 10, 12-15, 18-23 and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuwabara et al

Kuwabara et al (Molecular Cell, Vol. 2: 617-627, 1998) (provided in IDS filed 3-25-04) teach mammalian host cells and a method of making compositions (including a diagnostic composition) comprising an allosteric nucleic acid enzyme (maxizyme) comprising a cleavage active site that targets nucleotide sequences from BCR-ABL mRNA, which mRNA encodes a protein associated with cancer and which is an oncocyte marker, and which prevents apoptosis, and which nucleic acid enzyme further comprises a (cell/tissue specific) sensor site that binds to nucleotide sequences from an mRNA encoding a disease-associated protein, and which sensor binding sequences and target binding sequences are different nucleotide sequences, and which nucleic acid enzyme comprises regions that form a cavity to stably capture a Mg++ ion when binding a sensor site, and which nucleic acid enzyme further comprises a tRNA Val promoter sequence (of SEQ ID NO: 5) and an upstream pol III promoter sequence, which also comprises the nucleotide sequence 5"UUU3' and a termination sequence, and which nucleic acid construct is in an expression vector, and which composition further comprises a positively charged liposome for gene transfer. Kuwabara et al also

teach a method of specifically cleaving a target RNA using this nucleic acid enzyme construct in vitro (see abstract and last two full paragraphs on p. 617; figure 1 on p. 618; bridging paragraph, pp. 618-619; figure 2 on p. 619; bridging paragraph on pp. 619-620; bridging paragraph on pp. 620-621; bridging paragraph on pp. 621-622; first full paragraph on p. 622; figure 6 on p. 623; last full paragraph on p. 624; bridging paragraph on pp. 624-625; experimental procedures on p. 626).

Claims 1, 2, 4-8, 10, 12-15, 18-23 and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Tanabe et al

Tanabe et al (Biomacromolecules, Vol. 1: 108-117, 2000) (provided in IDS filed 3-25-04) teach mammalian host cells and a method of making compositions (including a diagnostic composition) comprising an allosteric nucleic acid enzyme (maxizyme) comprising a cleavage active site that targets nucleotide sequences from BCR-ABL mRNA, which encodes a protein associated with cancer and which is an oncocyte marker, and which prevents apoptosis, and which nucleic acid enzyme further comprises a (cell/tissue specific) sensor site which binds to nucleotide sequences from an mRNA encoding a disease-associated protein, and which sensor binding sequences and target binding sequences are different nucleotide sequences, and which nucleic acid enzyme comprises regions that form a cavity to stably capture a Mg++ ion when binding a sensor site, and which further nucleic acid enzyme further comprises a tRNA Val promoter sequence (of SEQ ID NO: 5) and an upstream pol III promoter sequence, and which also comprises the nucleotide sequence 5"UUU3' and a termination sequence, and which nucleic acid construct is in an expression vector, and which

composition further comprises a positively charged liposome for gene transfer. Tanabe et al also teach a method of specifically cleaving a target RNA in vitro using this nucleic acid construct (see abstract on p. 108, bridging paragraph pp. 108-109, first full paragraph on p. 109, bridging paragraph on pp. 109-110, figures 3 and 4 and text on pp. 111-112, text on p. 113).

Claims 1, 2, 4-8, 10, 12, 14, 15, 18-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Tanabe et al

Tanabe et al (Nature, Vol. 406: 473-474, 2000) (provided in IDS filed 3-25-04) teach mammalian host cells and a method of making compositions (including a diagnostic and pharmaceutical compositions) comprising an allosteric nucleic acid enzyme (maxizyme) comprising a cleavage active site that targets nucleotide sequences from BCR-ABL mRNA, which encodes a protein associated with cancer and which is an oncocyte marker, and which prevents apoptosis, and which nucleic acid enzyme further comprises a (cell/tissue specific) sensor site which binds to nucleotide sequences from an mRNA encoding a disease-associated protein, and which sensor binding sequences and target binding sequences comprise different nucleotide sequences, and which nucleic acid enzyme comprises regions that form a cavity to stably capture a Mg++ ion when binding a sensor site, and which further nucleic acid enzyme further comprises a tRNA Val promoter sequence (of SEQ ID NO: 5) and which nucleic acid construct is in an expression vector, and which composition further comprises a gene transfer vehicle. Tanabe et al also teach a method of specifically cleaving a target RNA in vitro and in vivo using this nucleic acid construct following in

vitro transduction of tumor cells and subsequently injecting these transduced tumor cells into NOD/SCID mice, whereby the nucleic acid enzyme is expressed in mice, target RNA is specifically cleaved, BCR-ABL expression is inhibited and tumor cell growth (metastasis) is inhibited in these mice (see entire document, which is a single page of text, esp. at paragraph bridging left, center and right columns for in vivo studies).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the

status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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11-24-04